Docket No. 455-023 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
JEFFREY S. KIEL, ET AL.	:	
Serial No.: 10/806,260	:	Group Art Unit: 1621
Filed: 03/22/2004	:	Valenrod, Yevgeny
For: **PHENOLIC ACID SALTS OF GABAPENTIN IN LIQUID AND/OR SEMI-SOLID DOSAGE FORMS AND METHODS OF USE**	:	

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE

Sir:

This document is being filed in response to the Office Action mailed on August 27, 2007.

Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim subject matter which Applicant regards as the invention. The Examiner indicates that the preamble of claim 33 claims a process for preparing gabapentin tannate while step (ii) requires directly incorporating

gabapentin tannate into a suitable pharmaceutical suspension dosage. The Examiner further states that step (ii) suggests that the Applicant is preparing a pharmaceutical composition of gabapentin tannate not gabapentin tannate itself.

The Examiner, however, incorrectly stated the preamble of claim 33 by selectively referring to just a portion of the preamble. The preamble in its entirety reads as follows:

> "A process for preparing gabapentin tannate to be used in a pharmaceutical composition for treating a condition of the central nervous system in a mammalian subject, comprising ..."

When one reads the preamble of claim 33 in its entirety, step (ii) relating to incorporating gabapentin tannate into a suitable pharmaceutical dosage form is not indefinite under 35 U.S.C. 112, second paragraph. The first element to be analyzed when rebutting a rejection based on indefiniteness is whether the claims, when read in view of the specification, are clear. If the Examiner does not provide sufficient reasoning as to why the claims are unclear when read in view of the specification, this element, which is critical to a *prima facie* case of indefiniteness, will not be established.

It is commonly accepted that a preamble may state the intended use or purpose of the invention. Patent Prosecution, Practice & Procedure Before the U.S. Patent Office, 2nd Edition, Irah H. Donner, The Bureau of National Affairs, Inc., Washington D.C. 2002, p. 908. Step (ii) of claim 33 recites a step for incorporating the newly formed "gabapentin tannate" into a pharmaceutical composition, as set forth in the preamble.

Further support for Applicants' assertion that claim 33 is definite under 35 USC 112 can be found where the specification of the present application states that the invention is a process for reacting gabapentin with tannic acid to produce a pharmaceutically effective amount of gabapentin tannate and processing the gabapentin tannate into suitable liquid and semi-solid dosage forms. (See page 2, lines 16-19). Further, on page 11, lines 3-5, it is stated that the gabapentin tannate salt

prepared according to the invention can then be directly incorporated into suitable pharmaceutically effective dosage forms without further purification and isolation.

Claims 1-29 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Chen et al.* (U.S. Patent No. 6,383,471), in view of *Gordziel* (U.S. Patent No. 6,287,597).

Applicants would first like to discuss the factual errors stated by the Examiner in his description of the scope of the prior art.

The Examiner incorrectly states that *Chen et al.* disclose the general teaching of converting an active pharmaceutical ingredient such as gabapentin (column 6, line 33) into its tannate salt complex (column 11, line 50).

The Examiner conveniently omits the description of the invention in the *Chen et al.* reference which is identified repeatedly throughout the *Chen et al.* disclosure. For example, the title of *Chen et al.* reads "Compositions and Methods for Improved Delivery of **Ionizable Hydrophobic Therapeutic Agents**". The Abstract also highlights that the present invention in *Chen et al.* "is directed to a pharmaceutical composition including a **hydrophobic therapeutic agent**." The Field of the Invention states that the invention relates to drug delivery systems, ... in particular ... for **the delivery of ionizable hydrophobic compounds** ... . The Background of the Invention discusses the problems of poor solubility associated with **hydrophobic therapeutic agents**. The Summary of the Invention indicates that an object of the present invention is to provide pharmaceutical compositions capable of solubilizing therapeutically effective amounts of **ionizable hydrophobic therapeutic agents**. The Detailed Description of the Preferred Embodiments reiterates the above statements and then at column 4, line 53, states that ionizable hydrophobic therapeutic agents are "compounds with little or no water solubility at neutral pH." The *Chen et al.* reference then further defines the ionizable hydrophobic therapeutic agents as having solubilities of less than about 1% by weight and typically less than about 0.1% or about 0.01% by weight (see column 4, lines 55-59). For the Examiner to state that *Chen et al.* disclose the general teaching of

converting an active pharmaceutical ingredient such as gabapentin into its tannate salt complex is just incorrect.

Gabapentin is not a hydrophobic therapeutic agent. Applicants can show that the Merck Index, 13th Edition, **attached hereto as Exhibit 1**, clearly defines gabapentin as having a solubility in water at pH 7.4 which exceeds 10%. Clearly, gabapentin was erroneously included in the laundry list of approximately 300 "hydrophobic therapeutic agents" in the *Chen et al.* patent. As will be discussed in further detail below, *Chen et al.* teach away from using a hydrophilic therapeutic agent such as gabapentin to form a tannate salt and thus cannot serve to create a *prima facie* case of obviousness. Also, submitted herewith is a Declaration of Richard Andrew Todebush, Ph.D., a person of ordinary skill in the pharmaceutical arts, wherein he opines as to the acceptance of the Merck Index as the "gold standard" for the pharmaceutical arts. Dr. Todebush also opines on the teachings of the *Chen et al.* patent ('471) and the *Gordziel* patent ('597) as they relate to the present claimed invention.

With regard to *Gordziel*, the Examiner is again factually incorrect when he states that *Gordziel* teaches a pharmaceutical composition that comprises: pyrilamine tannate, pectin, sucrose, saccharin sodium, magnesium aluminum silicate, water, glycerin, and methylparaben (column 3, Example 2). It is clear that the invention in *Gordziel* is defined as "a novel combination of **pyrilamine tannate and phenylephrine tannate**" which produces a composition having sympathomimetic decongestant and antihistaminic properties superior to the use of either one of the tannate compounds alone. See the "Abstract", "Field of the Invention", "The Invention" (column 2, lines 10-15) and "Claim 1". Tablets containing the novel combination of tannates are described in Example 1 and a suspension containing the novel combination of tannates is defined in Example 2. Both the tablets and suspension compositions are described as being prepared by conventional well known compounding techniques. The use of magnesium aluminum sulphate (MAS) in Example 2 has absolutely nothing to do with the formation of either pyrilamine tannate or phenylephrine tannate in *Gordziel*. The *Gordziel* reference itself states that pyrilamine tannate and phenylephrine tannate are prepared

by (1) reacting the antihistamine/decongestant free bases, e.g. phenylephrine and pyrilamine with tannic acid in the presence of a volatile solvent, usually isopropanol (see column 1, lines 60-64), or (2) alternative routes as described in U.S. Pat. Nos. 5,599,846 and 5,663,415 (see column 2, lines 4-6). Neither of the referenced patents discloses or in any way suggests the use of MAS in actually preparing the pyrilamine and phenylephrine tannate salts.

The Examiner then under the heading of "Obviousness" again incorrectly states that *Chen et al.* teach a method of producing gabapentin tannate. With regard to *Gordziel*, the Examiner again demonstrates that he does not understand that the present invention is the actual formation of the gabapentin tannate salt for use in a pharmaceutical composition. The MAS used in the present invention is to facilitate the formation of the gabapentin tannate salt not as a mere excipient in preparing the pharmaceutical composition. The invention of the present application as clearly defined in claim 1, is a process for preparing a gabapentin tannate to be used in a pharmaceutical composition by reacting gabapentin with tannic acid. The invention of the present application, as defined in independent claim 6, is recited as being a process for preparing gabapentin tannate by mixing tannic acid and a dispersing agent in a solvent to obtain a dispersion and then adding gabapentin to said dispersion. Claim 20 defines the invention as being a gabapentin tannate composition comprising as an active ingredient a pharmaceutically effective amount of gabapentin tannate. Claim 33 defines the invention as a process for preparing gabapentin tannate to be used in a pharmaceutical composition for treating a condition of the central nervous system in a mammalian subject, comprising: (i) reacting gabapentin with tannic acid to produce gabapentin tannate; and (ii) directly incorporating the gabapentin tannate into a suitable pharmaceutical suspension dosage form without further purification and isolation to yield a dosage form having a therapeutically effective amount of gabapentin tannate.

Considering now, that it is well established that the Examiner has the initial burden of presenting a *prima facie* case of obviousness, Applicants will demonstrate that the Examiner has failed to do so. The Examiner must show at least the following

three elements: (1) one or more of the cited references teach the claimed invention; with a (2) reasonable expectation of success; and (3) that the combination or modification of the prior art references would have been obvious to one of ordinary skill in the art. Failure to show any one of the foregoing elements will prevent the *prima facie* case of obviousness from being established.

With regard to element (1), there is no teaching of the claimed invention in the cited references either separately or combined. *Chen et al.* teach improving the solubility of a hydrophobic therapeutic agent by adding a carrier with an ionizing agent and a surfactant. As established above, gabapentin is not a hydrophobic therapeutic agent. The *Gordziel* reference teaches that pyrilamine tannate and phenylephrine tannate, already formed tannate salts, can be combined to produce a composition having superior therapeutic properties. The present invention as defined in independent claims 1, 6, 20, and 33 is a process (claims 1, 6, and 33) for making a tannate salt of gabapentin and the actual gabapentin tannate salt (claim 20). Accordingly, element (1) has not been established by the Examiner.

Referring now to element (2), i.e., that there be a reasonable expectation of success, Applicants again emphasize that *Chen et al.* lists gabapentin in a laundry list of over 300 suitable hydrophobic therapeutic agents and tannic acid in a laundry list of over 30 suitable acids. Even assuming, *arguendo*, that gabapentin is a hydrophobic therapeutic agent, there is nothing in *Chen et al.* or *Gordziel* that indicate a likelihood of success that a gabapentin tannate could be formed. Accordingly, element (2) has not been established by the Examiner.

Applicants have established above that the *Chen et al.* reference incorrectly identified gabapentin as a hydrophobic therapeutic agent with an intrinsic water solubility of less than about 1% by weight. Consequently, one of ordinary skill in the art, knowing that gabapentin is a hydrophilic therapeutic agent, would not be motivated by *Chen et al.* to select gabapentin to combine with tannic acid to produce gabapentin tannate. Furthermore, one of ordinary skill in the art would certainly not look to *Gordziel*

for excipients to use in the formation of any tannate salts of active pharmaceutical ingredients because *Gordziel* merely combines **already formed tannate salts** into a pharmaceutical composition. See Todebush Declaration, paragraphs 12. Thus, element (3) identified above has not been met.

It is the Examiner's position that one skilled in the art can just pick the compound of the claimed invention from the laundry list provided in *Chen et al.* Even assuming that gabapentin was a hydrophobic compound as defined by *Chen et al.*, what is conspicuously absent from the record is any reasonable expectation that one of ordinary skill in the art would be able to predict the formation of a gabapentin tannate salt based on either the *Chen et al.* or *Gordziel* references.

Merely identifying all of the elements of a claim or their equivalents in the prior art is not sufficient to establish a *prima facie* case of obviousness. Almost all inventions are combinations of old elements, and an Examiner may often find every element of the claimed invention in the prior art. If this finding were sufficient "to negate patentability, very few patents would ever issue." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Therefore, in order to establish a *prima facie* rejection for obviousness, an "Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would **[not** could] select the elements from the cited prior art references for combination in the manner claimed.

Consequently, independent claims 1, 6, 20 and 33, and all claims depending therefrom, are patentable over the cited references, taken alone or in combination. Additionally, Applicants assert that claim 6 is patentable taking into consideration that the Examiner readily admits that *Chen et al.* do not disclose or teach the use of a dispersing agent and Applicants have already established that *Gordziel* does not disclose or teach the use of a dispersing agent **in the formation of** any tannate salts of active ingredients. Again, *Gordziel* merely uses MAS in the preparation of a suspension containing **already formed** pyrilamine tannate and phenylephrine tannate, not in the

formation of either pryilamine tannate or phenylephrine tannate. Consequently, no *prima facie* case of obviousness has been established, and Applicants respectfully request reconsideration and withdrawal of the rejection.

With regard to claim 33, the Examiner indicates that claim 33 comprises steps (i) and (ii) which means that other steps such as purification steps can be included in the claim process. The Examiner completely disregards the wording in step (ii) which indicates that the gabapentin tannate formed in step (i) is incorporated into a suitable pharmaceutical suspension dosage form "without further purification and isolation to yield a dosage form having a therapeutically effective amount of gabapentin tannate". The Examiner states that because claim 33 is an open ended claim using the term "comprising" other steps such as purification steps can be included in the claim process, this is another factual error, when the wording of claim 33 clearly indicates that there are no further purification or isolation steps.

Applicants assert that the Examiner has failed to establish a *prima facie* case of obviousness for the reasons stated above. To summarize briefly, *Chen et al.* mistakenly identified gabapentin as a hydrophobic therapeutic agent when it is, in fact, a hydrophilic therapeutic agent. *Gordziel* has nothing to do with the formation of a gabapentin tannate salt and concerns itself only with the novel combination of pyrilamine tannate and phenylephrine tannate. With regard to claim 33, the Examiner further indicates that the Applicants have provided no showing of unexpected results arising from not purifiying the gabapentin tannate prior to incorporating it into a formulation. What the Examiner fails to appreciate is that unexpected results are only required to overcome a *prima facie* case of obviousness which the Examiner has failed to establish in the present case for the reasons stated above.

With regard to the Examiner's rejection of claims 1-4, 6, 8, 10-14, 19-35, 27 and 28 as being provisionally rejected under 35 U.S.C. 101 is claiming the same invention as that of claims 1-16 of co-pending application number 10/805,806. Applicants will

make the appropriate amendments to avoid double patenting once patentable subject matter has been determined.

Applicants would like the Examiner to note MPEP 707.07(f) which requires the Examiner to provide clear explanations of all actions taken by the Examiner. Where the Applicant traverses any rejection, the Examiner should, if he or she repeats the rejection, take note of applicant's argument and answer the substance of it.

In conclusion, Applicants assert that all pending claims 1-29 and 33 meet the formal and substantive requirements of the patent laws and are in condition for allowance. Accordingly, Applicants respectfully request early issuance of the formal Notice of Allowance.

Respectfully submitted,

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